PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference R 43494	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/004059	International filing date *(day/month/year)* 16.04.2004	Priority date *(day/month/year)* 17.04.2003
International Patent Classification (IPC) or national classification and IPC A61K39/395, C07K16/42, C12N15/63		
Applicant IGENEON KREBS-IMMUNTHERAPIE FORSCHUNGS- ... et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 09.11.2004	Date of completion of this report 22.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hermann, P Telephone No. +49 89 2399-7109

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004059

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-37 as originally filed

Sequence listings part of the description, Pages

1-8 as originally filed

Claims, Numbers

1-28 received on 05.02.2005 with letter of 02.02.2005

Drawings, Sheets

1/9-9/9 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☒ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☒ the claims, Nos. 28-34
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/004059

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: EP-A-0759442

2. The amendments filed with the response to the Written Opinion dated August 27th, 2003, within the prescribed time limit, do not introduce subject-matter which extends beyond the content of the application as filed, and therefore meet the requirements of Article 34(2)(b) PCT.

3. Novelty (Article 33(2) PCT)

3.1 None of the documents cited in the International Search Report discloses subject-matters falling within the respective scopes of claims 1-27 said claims meet therefore the requirements of Article 33(2) EPC.

4. Inventive step (Article 33(3) PCT)

4.1 Document D1 which discloses anti-idiotypic murine IgG2a antibodies (cf. D1 p. 43 last paragraph; p. 46 line 35 - p. 48 line 8; table XVI) is considered to represent the closest prior-art for the subject-matter of independent claim 1. The subject-matter of claim 1 differs from that of document D1 by the fact that the present antibody is a recombinant antibody having hamster or primate glycosylation. The effect linked to the presence of said glycosylation is i) in one example, that of mAb17-1A improving the ADCC measured in vitro with human effector cells and human cancer cell lines (cf. letter of reply paragraph bridging page 1 and 2), without however changing the immune response of rhesus monkey to said antibody (cf. description p.34 line 39 - p. 35 line 13 and p. 36 lines 27-32), whereas ii) in an other example, that of recombinant IgG2a Le-Y anti-idiotypic antibody, the presence of primate (human) glycosylation improves (increases) the immunogenicity of said antibody in Rhesus monkey (cf. p. 37 last §).

In view of D1 and as mentioned in the present application (cf. p. 8 lines 7-9), the problem to be solved by the present invention can be seen in the provision of monoclonal antibodies for use in pharmaceutical preparation, presenting improved immunogenic properties.

To note, according of common knowledge in the field the expression "improved immunogenic properties" means that the composition should, when used in passive immunization, induce less response from the immunized patient in order to be able to act, not to be rejected, and provide the expected effect; whereas when used in active immunization, said preparation should induce an improved humoral response from the vaccinated patient. Said improved humoral response would be characterized by higher titre of immunoglobulin directed against the antigenic determinants of the preparation, and presenting higher affinity for said antigenic determinants.

The solution to the herein above cited technical problem, i.e. the production of murine IgG2a recombinant antibodies in cells of primate or hamster species, does however appear to solve the problem in only very specific cases, i.e. that of recombinant IgG2a Le-Y anti-idiotypic antibody when produced in human cells, and an inventive step cannot be acknowledged on the entire scope of the claim.

Hence, the fact that recombinant mAb 17-1A used in passive immunization for targeting cancer cell and inducing ADCC, when produced in CHO cells induces a similar immunogenic response as when produced by hybridoma indicates that the problem has not been solved. Moreover, and in the absence of an indication to the contrary, the results obtained with recombinant mAb 17-1A produced in CHO indicate that the recombinant Le-Y anti-idiotypic IgG2a antibody when produced in CHO cells, given as a vaccine to Rhesus monkey, would certainly not present a better immunogenicity than the normal monoclonal antibody produced by the hybridoma cell line. Therefore, the International Preliminary Examining Authority is of the opinion that an inventive step for the product of claim 1 could have been eventually acknowledged only if the subject-matter of said claim had been limited to murine recombinant Le-Y anti-idiotypic IgG2a antibody produced in human cells, i.e. the only product for which a surprising effect (improved immunogenicity cf. p. 37 last §) has been demonstrated.

Therefore at present claim 1 does not meet the requirements of Article 33(3) PCT.

4.2 The same reasoning would apply for the subject-matter of dependent claims 2-15 which are referring to the subject-matter of independent claim 1, and claims 2-13 do not fulfill the requirements of Article 33(3) PCT.

4.3 The production of recombinant antibodies by genetic engineering is routine work for the skilled person. Therefore their method of production as those contained in claims 27-34 and the product required for performing said method such as vectors - e.g. commercially available multicistronic vectors such as those containing IRES elements, cell lines transformed with said vectors to express the expected product encoded by said vectors (i.e. recombinant antibody) are all well known in the art and are design procedures the skilled person would select in order to obtain the expected recombinant antibody. Hence the respective subject-matters of claims 16-27 do not appear to contain inventive steps and claims 16-27 do not meet the requirements of Article 33(3) PCT.

5. Further comments

5.1 The document P (WO-A-03/097663) cited in the international search report is not considered to be part of the prior art for the purposes of Article 33(2) and (3) PCT. However, should the present application enter the national or regional phase, and depending on the validity of the presently claimed priority, the above document could be relevant to the question of novelty [and inventive step].

5.2 Claim 2 lacks clarity (Article 6 PCT) due to the expression "antibody that contains an epitope specific for a tumor associated antigen". Said expression leaves the reader in doubt as to the exact scope of claim 2. To note, an antibody is either (a) directed against a tumor specific epitope or (b) might contain a mimotope which mimic a tumor specific epitope. Thus, if the meaning of the above mentioned expression corresponds to (b), the subject-matter of claim 2 is then redundant with the subject-matter of claim 3 and claims 2 and 3 lack then clarity (Article 6 PCT). The Preliminary International Examining Authority remains of the opinion that the use of the term "specific" in the expression "epitope specific for" leads to a lack of clarity of the subject-matter of claim 2, and claim 2 does not meet the requirements of Article 6 PCT.

5.3 Claim 1 lacks clarity (Article 6 PCT) because of the presence of the expression "at least a part of a murine IgG2a subtype amino acid sequence" in said claim. Hence it is not clear what is encompassed by "a part of" which can represent a single amino acid as well as a complete CDR.
Furthermore the description is silent as regards a clear definition concerning the sequence size and the characteristic of the murine IgG2a amino acid sequence which should be included in the recombinant antibody of claim 1.
Therefore claim 1 is unclear to such an extend that the establishment of an opinion as regards novelty, inventive step and industrial applicability of said claim on its entire scope is impossible.
The same objection as to lack of clarity (Article 6 PCT) arises for those claims which directly or indirectly depend on claim 1 and do not define clearly which "part of murine IgG2a subtype amino acid sequence" the recombinant antibody should encompass, i.e. present claims 2-27.